

## REVIEW

# New perspectives on natural flavonoids on COVID-19-induced lung injuries

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The SARS-CoV-2 virus, responsible for COVID-19, spread rapidly worldwide and became a pandemic in 2020. In some patients, the virus remains in the respiratory tract, causing pneumonia, respiratory failure, acute respiratory distress syndrome (ARDS), and sepsis, leading to death. Natural flavonoids (aglycone and glycosides) possess broad biological activities encompassing anti-inflammatory, antiviral, anti-tumoral, antiallergic, antiplatelet, and antioxidant effects. While many studies have focused on the effects of natural flavonoids in experimental models, reports based on clinical trials are still insufficient. In this review, we highlight the effects of flavonoids in controlling pulmonary diseases, particularly the acute respiratory distress syndrome, a consequence of COVID-19, and their potential use in coronavirus-related diseases. Furthermore, we also focus on establishing a relationship between biological potential and chemical aspects of related flavonoids and discuss several possible mechanisms of action, pointing out some possible effects on COVID-19.

## KEYWORDS

ACE2, acute lung injury, COVID-19, flavonoids, SARS-CoV-2

## 1 | INTRODUCTION

SARS-CoV-2 (Severe acute respiratory syndrome-related coronavirus type 2) infection is the cause of COVID-19 (coronavirus infectious disease), which spread rapidly worldwide, leading to widespread social fear, economic chaos, and many deaths. The World Health

Organization (WHO) declared this disease a pandemic on March 30, 2020, since COVID-19 reached more than 110 countries. The disease is considered a highly transmissible zoonosis in humans (Guo et al., 2020; Rothan & Byrareddy, 2020). It has an incubation period of 2 to 14 days, and after this period, the patient may remain asymptomatic or develop mild symptoms such as cough, fever, runny nose, and

myalgia. In some patients, if the virus remains in the respiratory tract, it can induce pneumonia, respiratory failure, acute respiratory distress syndrome (ARDS), and sepsis (Li et al., 2020; Zhou et al., 2020). The disease has a broad spectrum of symptoms and severity and can lead to death, especially if the patient has comorbidities (Singh, Gupta, & Misra, 2020; South, Diz, & Chappell, 2020). Current studies associate COVID-19 severity to the “cytokine storm” caused by the virus (Day, Fox, Halsey, Carpenter, & Kottaridis, 2020; Ye, Wang, & Mao, 2020). Once the virus evades the innate respiratory tract defense system, it reaches the lungs and induces an intense inflammatory response. Other studies suggest that the virus triggers a systemic disease by promoting hemophagocytosis through iron dissociation in the form of porphyria, justifying refractory hypoxemia (Wenzhong & Hualan, 2020). The scientific community eagerly seeks to develop a vaccine for prevention or drugs that treat and potentially cure the disease. While these measures are not yet resolved, alternatives to help fight symptoms must be found.

The use of natural products derived from herbs by folk medicine has been described for many years, and their properties are explored for new drug development. Several natural compounds have been described with scientifically proven therapeutic properties: antiviral, antiinflammatory, and antioxidant (Lago et al., 2014; Santana et al., 2016; Slader, Reddel, Jenkins, Armour, & Bosnic-Anticevich, 2006). In this context, flavonoids are classified as polyphenolic compounds metabolized by plants, fungi, and possess essential biological activities (Nijveldt et al., 2001). Knowing the chemical structure and effects of flavonoids on acute lung inflammation may lead to its application in clinical trials (as monotherapy or associated with known prescribed drugs). This review highlights the potential effects of several flavonoids in reducing acute pulmonary inflammation and ARDS, by inhibiting the enzymatic system associated with SARS-CoV-2.

## 2 | CORONAVIRUS, SARS-COV-2, COVID-19, AND ACUTE LUNG INFLAMMATION

The coronaviruses (CoVs) belongs to the Coronaviridae family, and is divided into four genera:  $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ , whereas only  $\alpha$ - and  $\beta$ -CoV are capable of infecting mammals (Guo et al., 2020). There are seven CoVs known to infect humans: HCoV-NL63, HCoV-OC43, HCoV-229E, HCoV-HKU1, MERS-CoV, and SARS-CoV-1 (Yin & Wunderink, 2018). The virus spike protein (S proteins) resembles a crown, in Latin called a corona, which named this family and is the main feature of CoVs (Schoeman & Fielding, 2019). The main selected proteins are the envelope protein—E, membrane protein—M, spike protein particles—S, and protein-encapsulated nucleus—N. The S protein is responsible for host cell recognition and membrane fusion. The N protein is responsible for binding the RNA genome, creating the nucleocapsid, and is associated with the replication process. The M protein determines the shape of the viral envelope, and the E protein, in smaller amounts, participates in the assembly and releases by budding (Chan et al., 2020; Schoeman & Fielding, 2019).

The coronavirus that affects humans is endemic and responsible for 15–30% of respiratory tract infections each year. However, in 2002, the SARS-CoV, a group 2b  $\beta$ -coronavirus, called the attention since it causes severe respiratory infection, the SARS outbreak in the Guangdong Province of China. Epithelial cells are the primary cells affected by SARS-CoV in the lung, although some studies showed that it can also affect dendritic cells and macrophages and induces proinflammatory cytokines that may contribute to the severe disease (Law et al., 2005; Peiris et al., 2003; Spiegel, Schneider, Weber, Weidmann, & Hufert, 2006). After 10 years, a novel CoVs appeared in the Middle East in 2012, provoking the Middle East Respiratory Syndrome-CoV (MERS-CoV) and induced respiratory infection in Saudi Arabia and other countries in the Middle East (Zaki, van Boheemen, Bestebroer, Osterhaus, & Fouchier, 2012). Unlike SARS-CoV, MERS-CoV uses the DPP4 (CD26) receptor to gain entry and effectively replicate in camel cell lines (Raj et al., 2013).

The first case of COVID-19 was reported in December 2019 in the city of Wuhan, China, and was called the new coronavirus SARS-CoV-2 (Rothan & Byrareddy, 2020). Many studies suggest that SARS-CoV-2 has arisen in bats, then infected an intermediate host (yet unknown), and suffered several mutations that allowed the virus to infect humans (Chan et al., 2020; Zhou et al., 2020). These authors showed that the new virus has 96% genomic similarity compared to the coronavirus residing in bats (Zhou et al., 2020). Human-to-human transmission occurs through coughing, sneezing, fecal-oral contact, and the virus can trigger respiratory, liver, renal, intestinal, and neurological system complications (Jin et al., 2020).

The SARS-CoV-2 has a single-stranded RNA genome with approximately 30 kb. This genetic material is translated into structural and non-structural proteins inside the host cell, determining its shape, life cycle, and virulence (Astuti and Ysrafil, 2020). In addition to the structures cited, SARS-CoV-2 also has the hemagglutinin esterase (HE) protein in the phospholipid double layer (Chan et al., 2020; Jin et al., 2020). Several studies point that the host cell angiotensin-converting enzyme 2 (ACE2) is the primary receptor for SARS-CoV-2 cell entry (Astuti and Ysrafil, 2020; Chan et al., 2020; Yan et al., 2020), as previously observed in SARS-CoV (Li et al., 2003). ACE2 is expressed in various organs such as the lungs, heart, brain, kidney, stomach, and liver (Hamming et al., 2004; Imai et al., 2005; Jiang, Gao, Lu, & Zhang, 2013; Olszanecki et al., 2009). Thus, tissue expression and ACE2 distribution are critical for infection and viral tropism. By interacting with ACE2 on cell surfaces, SARS-CoV-2 can connect with high affinity (Yan et al., 2020; Zhao et al., 2020), causing a generalized homeostasis imbalance that affects pulmonary, cardiac, circulatory, and renal systems, leading to systemic failure and eventually to patients death (Li, Li, Zhang, & Wang, 2020). When the virus binds to the ACE2 in the respiratory epithelium, the glycoprotein S inserts two subunits: S1, responsible for viral reach and tropism and S2, responsible for the fusion of the viral cell membrane. For this, the virus needs TMPRSS2 (serine transmembrane protease 2) to activate S glycoproteins in the viral envelope, thus associating SARS-CoV-2 and ACE2 in the lungs (Hoffmann et al., 2020; Wang, Grunewald, & Perlman, 2020). After membrane fusion, viral RNA replication begins,

which proceeds quickly toward cell death, endothelial and epithelial vascular leakage, and pro-inflammatory cytokines release (Jin et al., 2020). The viral RNA, identified as PAMPs (pathogen-associated molecular patterns) is detected by Toll-like (TLR) receptors (Birra et al., 2020) and thus starts a cascade, until activation of the nuclear transcription factor  $\kappa$ B (NF- $\kappa$ B) and consequent release of several systemic inflammatory mediators occurs in the lungs (Alexopoulou, Holt, Medzhitov, & Flavell, 2001; Wu & Chen, 2014). When SARS-CoV-2 infection occurs, there is a decrease in ACE2 and an increase in angiotensin II. Reduction of ACE2 is known to be related to alveolar injury and increased vascular permeability (Imai et al., 2005), and it was confirmed in experimental animal models (Imai, Kuba, & Penninger, 2008; Ye & Liu, 2020). In addition, angiotensin I (mild vasoconstrictor) is converted by ACE to angiotensin II, a potent vasoconstrictor. ACE2 converts angiotensin II to angiotensin 1–7, known for its vasodilatory effects (Benigni, Cassis, & Remuzzi, 2010). The ACE2 is also expressed in significant amounts in the pericyte, a mesenchymal cell presented in the endothelium of small vessels, which are essential for endothelial stability. When SARS-CoV-2 attacks the vascular system, there is endothelial imbalance and consequent dysfunction in the microcirculation (Chen, Li, Chen, Feng, & Xiong, 2020). The autopsy of fatal COVID-19 patients reveals the presence of a microthrombi (Dolhnikoff et al., 2020) that can cause the severe form of COVID-19.

Angiotensin II can bind to angiotensin receptors 1 (AT1) and 2 (AT2) that regulate hemodynamic stability and blood pressure (Arendse et al., 2019; Kreutz et al., 2020). AT1 has a vasoconstrictor effect and accounts for increased vascular permeability inducing inflammation and remodeling (Benigni et al., 2010). AT2 receptors, on the other hand, have a vasodilatory effect and exert anti-regulatory activity for AT1 (Batenburg, Tom, Schuijt, & Danser, 2005). One hypothesis is that angiotensin II production through AT1 receptors activates the Janus kinase signal transducer and activator of transcription pathways involved in pro-inflammatory, proliferative, and pro-fibrotic responses and activates other pathways such as reactive oxygen species production, cell growth, and apoptosis (Seif et al., 2020). The increase in angiotensin II, on the other hand, was related to increased inflammatory activity due to the vital role of AT1 and the recruitment of immune system cells (Forrester et al., 2018).

Lung inflammation is one of the characteristics of several lung diseases such as asthma, chronic obstructive lung diseases, and others (Moldoveanu et al., 2009). However, acute lung inflammation and the ARDS are characterized by an intense inflammation that still kills more than 40% of the patients in the intensive therapy care unit (Bellani et al., 2016).

Acute lung injury (ALI) is characterized by the recruitment of immune cells, neutrophils, macrophages, and lymphocytes, with a high cytokine production such as IL-6, IL-1 $\beta$ , and TNF- $\alpha$  (Bittencourt-Mernak et al., 2017; Herold, Mayer, & Lohmeyer, 2011). Currently, several experimental animal models mimic inflammatory findings in ALI, such as intratracheal instillation lipopolysaccharide (LPS), viral infection, and sepsis (Bittencourt-Mernak et al., 2017; Rungtung et al., 2018; Zhang et al., 2017).

It is described that COVID-19 patient developed a cascade of cytokines and that the immune system often does not respond promptly (Ye et al., 2020). This SARS-CoV-2/ACE2 linkage triggers an exaggerated cytokine response, and consequently, an exacerbated inflammatory process, called “cytokine storm” (Jin et al., 2020; Ye et al., 2020). There is still a dysfunction of the renin-angiotensin system with increased inflammation and vascular permeability, resulting in reduced ACE2 function (Basu, Sarkar, & Maulik, 2020; Li, Li, et al., 2020). Therefore, there is a systemic immune imbalance with significant systemic repercussions.

Respiratory symptoms and pulmonary effects in patients with COVID-19 are the most discussed features related to severity. Three possibilities have been described regarding manifestations of the disease when it affects the respiratory tract of symptomatic patients: (1) the virus remains in the upper respiratory tract, and due to viral replication, the patient may present symptoms such as sore throat, dry cough, and runny nose; (2) the patient has worsened respiratory symptoms, including dyspnea, hypoxemia, and fever due to the exacerbated immune response; (3) one-third of patients evolve to respiratory failure such as ARDS and need rapid ventilation support (Rothan & Byrareddy, 2020).

The pathogenesis of COVID-19 is highly complex and involves suppressing host antiviral and innate immune response, induction of oxidative stress followed by hyper inflammation described as the “cytokine storm,” causing ALI, tissue fibrosis, and pneumonia. Most patients that recovered from severe COVID-19 showed elevated lung disease severity at days 10–14 after initial symptoms presentations. The lung lesions can be absorbed in 53.0% of patients during the third week after discharge, with no sequelae. However, about 40% of patients had lung ground-glass opacity (GGO) and fibrous stripe as the main manifestations upon computed tomography images, seen on radiological follow-ups (Pan et al., 2020).

There is an increase in the cytokines TNF- $\alpha$ , IL-1 $\beta$ , IL-7, IL-8, IL-9, IL-10, INF- $\gamma$ , monocyte chemoattractant protein-1, and others (Burgos-Blasco et al., 2020; Ye et al., 2020). Most COVID-19 patients, especially among elderly patients, had marked lymphopenia and increased neutrophils, but T cell counts in severe COVID-19 patients surviving the disease were gradually restored (Akbari et al., 2020; Chen et al., 2020). Some critically ill patients showed higher expressions of IL-1 $\beta$ , IL-6, TNF- $\alpha$ , and other cytokines (Akbari et al., 2020). Thus, these inflammatory-related factors might function as a biomarker to monitor the progression of COVID-19 disease.

Some new reports showed that COVID-19 survivors, particularly those developing the severe form, evolved to pulmonary fibrosis (Rogliani et al., 2020; Zhang et al., 2020). Interestingly, Aloufi et al. (2020) reported that lung fibroblasts isolated from idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease patients express higher levels of ACE2. It suggested that the risk of developing pulmonary fibrosis can be associated with increased expression of ACE2, which occurred in the risk group, involving obesity, heart, and aging disorders (Aloufi et al., 2020).

As discussed above, viruses commonly encode proteins that inhibit the immune system, promote viral invasion, and pathogenesis.

In this context, flavonoids have been studied for their antiviral effect and inhibition of the virus membrane proteins, preventing cellular invasion (Russo, Moccia, Spagnuolo, Tedesco, & Russo, 2020; Seong, Kim, & Shin, 2018). Although several studies have shown that different flavonoids are beneficial in controlling respiratory diseases, additional studies of the specific effects of flavonoids on molecular mechanisms in lung diseases are needed.

In this review, we focused on flavonoids described in the literature as having potential biological effects against different coronavirus (SARS-CoV and MERS), respiratory illnesses such as ALI, and ARDS, and those flavonoids showing antioxidant and antiinflammatory properties, focusing on possible relation of the flavonoids' chemical structure and biological function. We also discussed, based on these pieces of evidence, the potential application of flavonoids to SARS-CoV-2 and COVID-19.

### 3 | FLAVONOIDS: CHEMISTRY, OCCURRENCE, ANTIINFLAMMATORY, AND ANTIVIRAL POTENTIAL ACTION

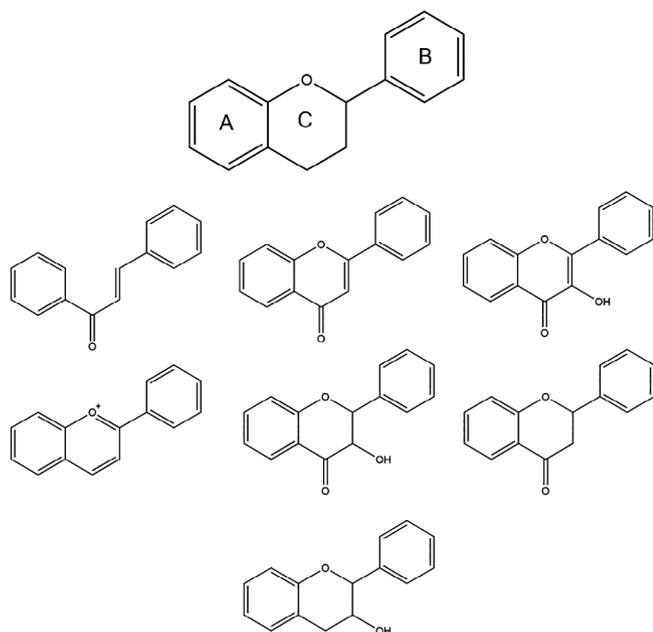
The flavonoids play an essential role among natural products, comprising more than 8,000 different bioactive molecules described in the literature. These metabolites are present in many plant species, including various products and grains (Jucá et al., 2020). Flavonoids are chemically characterized by a general structure of a 15-carbon skeleton with two phenyls (rings A and B) and one heterocyclic (ring C) unities, also known as  $C_6C_3C_6$  (Figure 1). This class's subgroups include chalcones, flavones, flavonols, flavanones, flavanonols, flavans, anthocyanins, and isoflavonoids (Figure 2), which can contain one or

more carbohydrate moieties (glycosylated flavonoids) or is composed exclusively by aglycones.

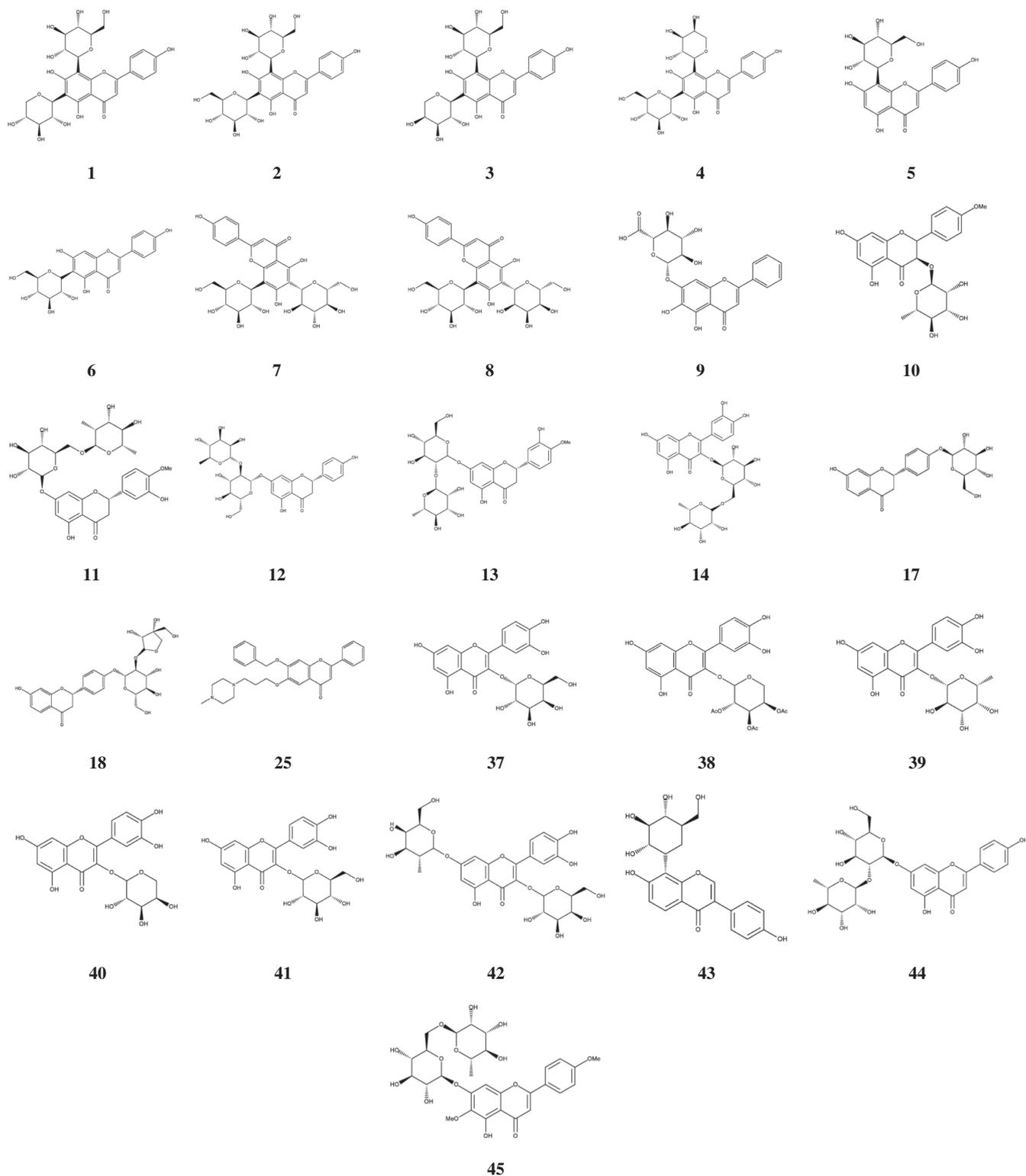
Several biological properties have been described for these compounds, including antioxidant, antiaging, antiinflammatory, immunomodulatory, cardioprotective, antimicrobial, antifungal, and antiviral activities (Brendler et al., 2020; Jucá et al., 2020; Lago et al., 2014; Santana et al., 2016). As such, these compounds are of interest in the treatment of various illnesses. Several studies with flavonoids have been published, involving pathologies such as viral SARS, ALI and ARDS (Bittencourt-Mernak et al., 2017; Jo, Kim, Kim, Shin, & Kim, 2019; Zhang et al., 2017); however, to the best of our knowledge, no previous research articles were published until now showing the effects of flavonoids in COVID-19. However, other authors review the literature to suggest the potential use of flavonoids in COVID-19 (Russo et al., 2020; Solnier & Fladerer, 2020; Tutunchi, Naeini, Ostadrahimi, & Hosseinzadeh-Attar, 2020). Many unique features of flavonoids, such as antioxidant and antiinflammatory properties, their ability to inhibit enzymes, to destroy cell membranes, and to prevent virus penetration make them suitable for further tests to demonstrate their beneficial effects against these diseases (Jucá et al., 2020; Nijveldt et al., 2001; Panche, Diwan, & Chandra, 2016).

The leaves of *Micocos paniculate*, also known as shiral (India, Bengal), has been traditionally used to treat upper airway infections, containing flavonoids such as apigenin C-glycosides (ACGs), vicenin-1 (1), vicenin-2 (2), isoshaftoside (3), shaftoside (4), vitexin (5), isovitexin (6), violanthin (7), and isoviolanthin (8) (Li et al., 2018). Their effects were measured by cytokine level determination and lung inflammation evaluation in situ. ACGs reduced pulmonary edema and microvascular permeability by down-regulating LPS-induced TNF- $\alpha$ , IL-6, and IL-1 $\beta$  expression. Metabolic profiling showed that this protective effect was due to suppression of TLR4/TRPC signaling pathway activation. As such, ACGs could be further explored to treat ALI and ARDS.

Obtained from *Scutellaria baicalensis*, baicalin (9) has shown anti-apoptosis, antiinflammatory, and antioxidant properties. An in vitro study demonstrated that this compound attenuates oxidative stress and endothelial dysfunction by improving ACE2 activity (Wei et al., 2015). Improved endothelial function impaired Ang II by promoting endothelial-dependent vasodilation and suppression of human umbilical vein endothelial cells apoptosis. Baicalin decreased the expression of pro-apoptotic protein Bax and cleaved caspase-3, involving an increase of Bcl-2 expression. Baicalin also significantly converted Ang II to Ang-(1-7) by ACE2 and Mas receptor mRNA expression and protein expression and up-regulation of the PI3K/AKT/eNOS pathway (Wei et al., 2015). Astilbin (10), found in *Smilax china*, shown to diminish LPS-induced ARDS in vivo and in vitro successfully. This effect was determined by regulating pro-inflammatory cytokines TNF- $\alpha$  and IL-6, MAPK phosphorylation inhibition, suppression of proinflammatory enzyme heparinase, and diminished heparin sulphate degradation (Kong et al., 2016). Glycosylated flavonoids hesperidin (11), naringin (12), and neohesperidin (13), found in different quantities in citrus fruits, were among the compounds subjected to a molecular docking study. The SARS-CoV S protein has a significant binding affinity to the human ACE2 enzyme, considered to be crucial



**FIGURE 1** General and subgroup structures of the flavonoids class

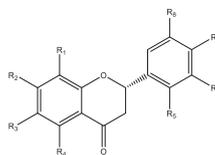


**FIGURE 2** Chemical structure of flavonoids 1–101. (a) Chemical structure of glycosylated flavonoids; (b) Chemical structure of free flavonoids; and (c) Chemical structure of theaflavins and procyanidin derivatives

for virus entrance in host cells (Basu et al., 2020). Therefore, compounds that bind this enzyme could prevent coronavirus infection.

Rutin (14) was investigated for antiinflammatory effects in vivo (Guardia, Rotelli, Juarez, & Pelzer, 2001). At a dosage of 80 mg/kg it

was able to decrease paw edema in the acute phase of inflammation (day six) as well as in the chronic phase (days 7 to 30). On days 21st and 30th after induced inflammation, rutin could suppress this effect by 100%. Comparatively, related flavonoids quercetin (15) and



**16**  $R_1=R_3=R_4=R_5=R_6=R_8=H$ ,  $R_2=R_7=OH$

**20**  $R_1=R_3=R_5=R_6=H$ ,  $R_2=R_4=R_7=R_8=OH$

**27**  $R_1=R_3=R_5=R_6=R_7=R_8=H$ ,  $R_2=R_4=OH$

**36**  $R_1=R_3=R_5=R_6=R_8=H$ ,  $R_2=OMe$ ,  $R_4=R_7=OH$

**46**  $R_1=R_3=R_4=R_8=H$ ,  $R_2=R_4=R_6=OH$ ,  $R_7=OMe$

**79**  $R_1=R_5=R_6=H$ ,  $R_2=R_4=R_7=OH$ ,  $R_3=geranyl$ ,  $R_8=OMe$

**80**  $R_1=R_5=R_6=H$ ,  $R_2=R_4=OH$ ,  $R_3=geranyl$ ,  $R_7=R_8=OMe$

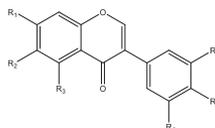
**81**  $R_1=R_5=R_6=R_8=H$ ,  $R_2=R_4=R_7=OH$ ,  $R_3=geranyl$

**82**  $R_1=R_5=R_6=H$ ,  $R_2=R_4=R_7=R_8=OH$ ,  $R_3=geranyl$

**83**  $R_1=R_5=H$ ,  $R_2=R_4=R_7=OH$ ,  $R_3=geranyl$ ,  $R_6=R_8=OMe$

**84**  $R_1=R_5=R_6=R_8=H$ ,  $R_2=OMe$ ,  $R_3=geranyl$ ,  $R_7=OH$

**24**  $R_1=R_3=R_5=R_6=R_8=H$ ,  $R_2=R_4=R_7=OH$



**19**  $R_1=R_3=R_4=R_6=H$ ,  $R_2=R_5=OH$

**21**  $R_1=R_3=R_5=OH$ ,  $R_2=R_4=R_6=H$

**85**  $R_1=R_5=OH$ ,  $R_2=R_3=R_4=H$ ,  $R_7=prenyl$

**87**  $R_1=R_3=R_4=H$ ,  $R_2=R_6=OH$ ,  $R_5=geranyl$

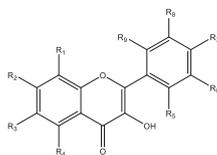
**88**  $R_1=R_5=OH$ ,  $R_2=R_3=R_4=H$ ,  $R_7=geranyl$

**FIGURE 2** (Continued)

hesperidin (**11**) were also tested and showed smaller significant antiinflammatory properties. A study conducted with licorice flavonoids liquiritigenin (**16**), liquiritin (**17**), and liquiritin apioside (**18**) from *Glycyrrhiza uralensis* showed that these compounds effectively diminish LPS-induced pulmonary inflammation by inhibiting inflammatory cell infiltration and inflammatory mediator release, including reduction of TNF- $\alpha$  and IL-1 $\beta$  expression. The maximal dosage of those flavonoids (30 mg/kg) produces similar effects as treatment with dexamethasone at 1 mg/kg, the standard drug used for the assays (Xie, Dong, Wu, Yan, & Xie, 2009). These results were consistent with the effects observed in macrophages for daidzein (**19**), eriodictyol (**20**), genistein (**21**), isorhamnetin (**22**), pelargonidin (**23**), and naringenin (**24**) (Hämäläinen, Nieminen, Vuorela, Heinonen, & Moilanen, 2007).

The antiinflammatory and antioxidant properties of eriodictyol (**20**) were also studied in the LPS-induced ALI model. Eriodictyol demonstrated inhibition of proinflammatory cytokine expression and attenuation of oxidative injury by activating the Nrf2 pathway at a dose of 30 mg/kg (Zhu, Guo, Huang, Wu, & Zhang, 2015). Besides the effects antiinflammatory of naringenin (**24**), these flavonoids also demonstrated an inhibition of the 3-chymotrypsin-like protease (3CLpro), and reduction of ACE receptors activity (Tutunchi et al., 2020).

The in vivo protective effect of synthetic flavonoid LFG-500 (**25**) was shown to inhibit cytokines such as TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 in lung tissues after inducing ALI and inflammation by LPS challenge. In vitro effects were investigated as well, where the cytokine inhibition was also observed, by inhibiting NF- $\kappa$ B activation. In addition, p38 and



**22** R<sub>1</sub>=R<sub>3</sub>=R<sub>5</sub>=R<sub>6</sub>=R<sub>9</sub>=H, R<sub>2</sub>=R<sub>4</sub>=R<sub>7</sub>=OH, R<sub>8</sub>=OMe

**31** R<sub>1</sub>=R<sub>3</sub>=R<sub>5</sub>=R<sub>6</sub>=R<sub>8</sub>=H, R<sub>2</sub>=R<sub>4</sub>=R<sub>7</sub>=R<sub>9</sub>=OH

**32** R<sub>1</sub>=R<sub>3</sub>=R<sub>5</sub>=R<sub>9</sub>=H, R<sub>2</sub>=R<sub>4</sub>=R<sub>6</sub>=R<sub>7</sub>=R<sub>8</sub>=OH

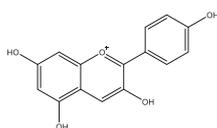
**33** R<sub>1</sub>=R<sub>3</sub>=R<sub>4</sub>=R<sub>5</sub>=R<sub>8</sub>=R<sub>9</sub>=H, R<sub>2</sub>=R<sub>6</sub>=R<sub>7</sub>=OH

**34** R<sub>1</sub>=R<sub>5</sub>=R<sub>6</sub>=R<sub>8</sub>=R<sub>9</sub>=H, R<sub>2</sub>=R<sub>3</sub>=R<sub>4</sub>=R<sub>7</sub>=OH

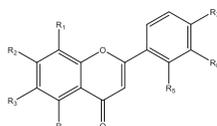
**60** R<sub>1</sub>=R<sub>2</sub>=R<sub>4</sub>=R<sub>7</sub>=OH, R<sub>3</sub>=R<sub>5</sub>=R<sub>6</sub>=R<sub>8</sub>=R<sub>9</sub>=H

**65** R<sub>1</sub>=R<sub>5</sub>=R<sub>9</sub>=H, R<sub>2</sub>=R<sub>4</sub>=R<sub>6</sub>=R<sub>7</sub>=OH, R<sub>3</sub>=R<sub>8</sub> = prenyl

**100** R<sub>1</sub>=R<sub>3</sub>=R<sub>5</sub>=R<sub>6</sub>=R<sub>8</sub>=R<sub>9</sub>=H, R<sub>2</sub>=R<sub>4</sub>=R<sub>7</sub>=OH



**23**



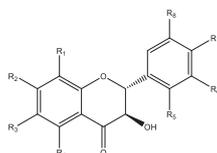
**26** R<sub>1</sub>=R<sub>3</sub>=R<sub>5</sub>=H, R<sub>2</sub>=R<sub>4</sub>=R<sub>6</sub>=R<sub>7</sub>=OH

**28** R<sub>1</sub>=R<sub>5</sub>=R<sub>6</sub>=R<sub>7</sub>=H, R<sub>2</sub>=R<sub>4</sub>=OH, R<sub>3</sub>=OMe

**29** R<sub>1</sub>=R<sub>3</sub>=R<sub>5</sub>=R<sub>6</sub>=H, R<sub>2</sub>=R<sub>4</sub>=R<sub>7</sub>=OH

**30** R<sub>1</sub>=R<sub>3</sub>=R<sub>5</sub>=R<sub>6</sub>=R<sub>7</sub>=H, R<sub>2</sub>=R<sub>4</sub>=OH

**15** R<sub>1</sub>=R<sub>3</sub>=R<sub>5</sub>=R<sub>6</sub>=H, R<sub>2</sub>=R<sub>4</sub>=R<sub>7</sub>=R<sub>8</sub>=OH



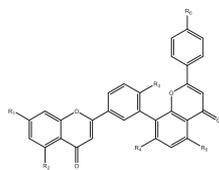
**35** R<sub>1</sub>=R<sub>3</sub>=R<sub>4</sub>=R<sub>5</sub>=R<sub>6</sub>=H, R<sub>2</sub>=R<sub>7</sub>=R<sub>8</sub>=OH

**77** R<sub>1</sub>=R<sub>5</sub>=R<sub>6</sub>=H, R<sub>2</sub>=R<sub>4</sub>=R<sub>7</sub>=R<sub>8</sub>=OH R<sub>3</sub> = geranyl

**78** R<sub>1</sub>=R<sub>5</sub>=R<sub>6</sub>=H, R<sub>2</sub>=R<sub>4</sub>=R<sub>8</sub>=OH, R<sub>3</sub> = geranyl, R<sub>7</sub>=OMe

**89** R<sub>1</sub>=R<sub>3</sub>=R<sub>5</sub>=H, R<sub>2</sub>=R<sub>4</sub>=R<sub>6</sub>=R<sub>7</sub>=R<sub>8</sub>=OH

**FIGURE 2** (Continued)

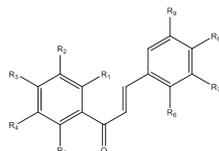


**47**  $R_1=R_2=R_3=R_4=R_5=R_6=OH$

**48**  $R_1=R_2=R_4=R_5=R_6=OH, R_3=OMe$

**49**  $R_1=R_3=OMe, R_2=R_4=R_5=R_6=OH$

**50**  $R_1=R_3=R_6=OMe, R_2=R_4=R_5=OH$



**51**  $R_1=R_2=R_6=R_7=R_9=H, R_3=OMe, R_4 = \text{prenyl}, R_5=R_8=OH$

**52**  $R_1=R_2=R_6=R_7=R_9=H, R_3=R_5=R_8=OH, R_4=\text{geranyl}$

**53**  $R_1=R_2=R_6=R_7=R_9=H, R_3=R_5=R_8=OH, R_4=\text{geranyl}$

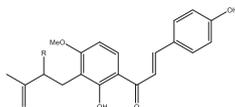
**59**  $R_1=R_2=R_6=R_7=R_9=H, R_3=R_5=R_8=OH, R_4 = \text{prenyl}$

**61**  $R_1=OMe, R_2=R_4=R_5=R_6=R_7=R_9=H, R_3=R_5=R_8=OH$

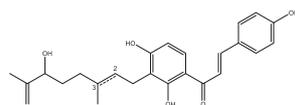
**62**  $R_1=R_3=R_8=OH, R_2=R_5=R_6=R_7=R_9=H, R_4= \text{prenyl}$

**63**  $R_1=R_4=R_8=R_9=H, R_2= \text{prenyl}, R_3=R_5=R_6=R_7=OH$

**86**  $R_1=R_8=OH, R_2=R_5=R_6=R_7=R_9=H, R_3= OMe, R_4 = \text{prenyl}$

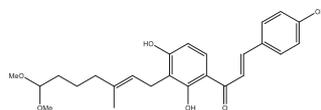


**54**  $R = OH$



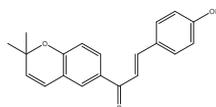
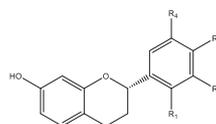
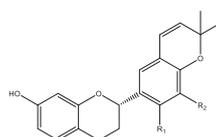
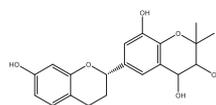
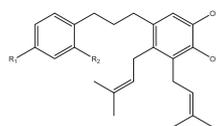
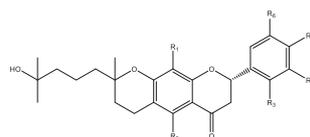
**56**  $\Delta^{2-3}$

**57**



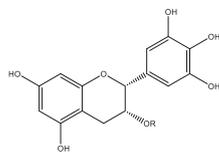
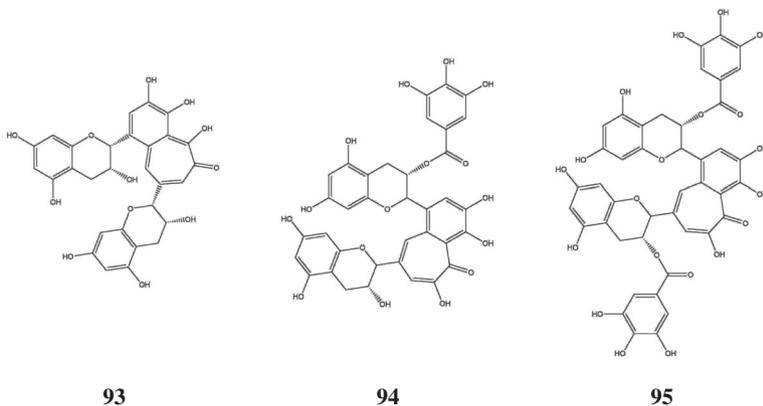
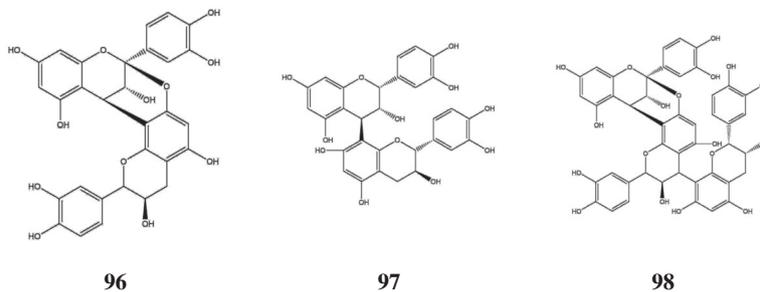
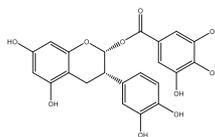
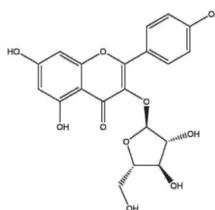
**58**

**FIGURE 2** (Continued)

**64****66** R<sub>1</sub>=H, R<sub>2</sub>=R<sub>3</sub>=OH, R<sub>4</sub>=prenyl**67** R<sub>1</sub>=R<sub>4</sub>=prenyl, R<sub>2</sub>=R<sub>3</sub>=OH**68** R<sub>1</sub> = prenyl, R<sub>2</sub> = OH**69****70** R<sub>1</sub>=R<sub>2</sub>=OH**71** R<sub>1</sub>=OH, R<sub>2</sub>=OMe**72** R<sub>1</sub>=R<sub>3</sub>=R<sub>4</sub>=H, R<sub>2</sub>=R<sub>5</sub>=R<sub>6</sub>=OH**73** R<sub>1</sub>= R<sub>3</sub>=R<sub>4</sub>=R<sub>7</sub>=H, R<sub>2</sub>=R<sub>6</sub>=OH, R<sub>5</sub>=OMe**74** R<sub>1</sub>=R<sub>3</sub>=R<sub>7</sub>=H, R<sub>2</sub>=OH, R<sub>4</sub>=R<sub>5</sub>=R<sub>6</sub>=OMe**75** R<sub>1</sub>=R<sub>3</sub>=R<sub>7</sub>=H, R<sub>2</sub>=R<sub>5</sub>=OH, R<sub>4</sub>=R<sub>6</sub>=OMe**76** R<sub>1</sub>=R<sub>3</sub>=H, R<sub>2</sub>=R<sub>5</sub>=R<sub>7</sub>=OH, R<sub>4</sub>=R<sub>6</sub>=OMe**FIGURE 2** (Continued)

JNK MAPK pathways were found to be involved in the antiinflammatory properties of compound **25** (Li et al., 2016). According to a review reporting effects of flavonoids in lung diseases, luteolin (**26**), pinocembrin (**27**), and oroxylin-A (**28**) were described to attenuate LPS-induced ARDS in vivo and in vitro, affecting proinflammatory cytokine concentrations as well as MAPK and NF- $\kappa$ B

pathway activation (Kimata et al., 2000). In addition, the therapeutic effect of oroxylin-A (**28**) ameliorated the increased of the white blood cells counts, elevated plasma tumor necrosis factor (TNF)- $\alpha$ , and nitric oxide (NO), increased pulmonary edema, thickened alveolar septa caused by the administration of LPS (Tseng et al., 2012). In vitro pretreatment with pinocembrin (**27**) remarkably regulated the production

**90** R=3,4,5-trihydroxybenzoate**91** R= H**92** R=3,4,5-trihydroxybenzoate**93****94****95****96****97****98****99****101****FIGURE 2** (Continued)

of TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and IL-10 via inhibition of I $\kappa$ B $\alpha$ , ERK1/2, JNK, and p38 MAPK phosphorylation. In the mouse model of LPS-induced ALI, pinocembrin (20 or 50 mg/kg, i.p.) attenuated the development of pulmonary edema, histological severities, as well as neutrophil,

lymphocyte, and macrophage infiltration, increased by LPS administration (Soromou et al., 2012).

Other flavonoids were reported to affect the expression of additional pro-inflammatory genes such as nitric oxide synthase,

cyclooxygenase, and lipoxygenase. Luteolin (**26**), apigenin (**29**), and chrysin (**30**) were among those with inhibitory potential against iNOS and NO products. Morin (**31**) and myricetin (**32**) were cited for the ability to affect the lipoxygenase enzyme (Havsteen, 2002; O'Leary et al., 2004; Yoon & Baek, 2005). Flavonoids **26**, **29–31** also inhibit the enzyme cyclooxygenase. Furthermore, luteolin, apigenin, and fisetin (**33**) were shown to inhibit the synthesis of cytokines IL-4 and IL-13 in vitro (Hirano et al., 2004). Scutellarein (**34**) and fustin (**35**) were also among the flavonoids able to inhibit IL-4. Compounds **26**, **29**, **31**, **32**, and **34** were reported to have antiinflammatory effects against asthma models and chronic obstructive pulmonary disease (Coutinho, Muzitano, & Costa, 2009; Kim, Son, Chang, & Kang, 2004; O'Leary et al., 2004). Another study showed that pre-treatment with luteolin decreased lung edema and protein content in lung tissue and bronchoalveolar lavage fluid (BALF). Furthermore, luteolin pre-treatment showed a significant reduction in proinflammatory cytokines (IL-6 and IL-1 $\beta$ ) and attenuation in sepsis-induced ALI in mice through the suppression in ICAM-1, NF- $\kappa$ B, oxidative stress, and partially iNOS pathways (Rungsung et al., 2018). In addition, Kuo et al. (2011) investigated the protective effects and luteolin mechanisms in intratracheal instillation of LPS-induced ALI in mice. The antioxidant and antiinflammatory effects of luteolin were observed by reducing catalase and superoxide dismutase activities, the levels of oxidative damage and lipid peroxidation, and the secretion of TNF- $\alpha$ , IL-8 (KC), and ICAM-1 in BALF after LPS-induced ALI. Furthermore, the pre-treatment with luteolin restored the LPS-induced decrease in oxygen pressure and increase of carbon dioxide in arterial blood.

Antiinflammatory effects of morin (**31**) on ALI were studied using LPS-induced ALI mouse model. Morin showed attenuation in the inflammatory cells and decreased IL-1 $\beta$ , IL-18, and IL-6 cytokines. This flavonoid also decreased lung NLRP3 inflammasome protein levels and improved superoxide dismutase activity (Tianzhu, Shihai, & Juan, 2014).

Fisetin (**33**), a flavonoid found in several fruits and vegetables, effectively reduced the IL-6 and TNF- $\alpha$  release and total protein in BALF, besides improving lung inflammation. In addition, fisetin is related to the inhibition of the Toll-like receptor 4 (TLR4) and NF- $\kappa$ B expression (Feng, Jiang, Sun, Fu, & Li, 2016).

Sakuranetin (**36**), from the Brazilian plant *Baccharis retusa*, exhibited antiinflammatory activity, significantly reducing the number of neutrophils. In addition, sakuranetin reduced the number of macrophages in bronchoalveolar lavage fluid (BALF) and pro-inflammatory cytokines like IL-1 $\beta$ , IL-8, and TNF- $\alpha$  in mice exposed to LPS instillation (Bittencourt-Mernak et al., 2017). These authors showed that sakuranetin could similarly act as an immunomodulatory compound since it was reported that this treatment in mice could modulate the macrophage profile. In addition, sakuranetin has an inhibitory effect in viral RNA synthesis, effective in the inactivation of the influenza B/Lee/40 virus, and could be a good candidate for treating diseases related to the influenza virus (Kwon, Ji, Yim, Kim, & Choi, 2018).

The  $\beta$ -CoVs, like SARS-CoV-2, usually induce the production of polypeptides with  $\sim$ 80 kDa after the genome transcription. This polypeptide is cleaved to generate various proteins through proteolytic

processes, mediated by two proteins: papain-like protease (PL<sup>PRO</sup>) and 3-chymotrypsin-like protease (3CL<sup>PRO</sup>). PL<sup>PRO</sup> and 3CL<sup>PRO</sup> are crucial to the virus life cycle and viral coronavirus replication (Lin et al., 2005; Nguyen et al., 2012; Park et al., 2016). As such, they are viable targets for developing drugs against SARS, MERS, and other coronavirus infections (Chen et al., 2006; Lin et al., 2005; Nguyen et al., 2012). The SARS-CoV PL<sup>PRO</sup> catalytic domain comprises various catalytically active enzymes, transmembrane domains, and domains with unknown function. The associated membrane domain can perform proteolytic cleavage releasing proteins nsp1, nsp2, and nsp3 from the viral polyprotein, which is essential for viral replication. This protease is also a deubiquitinating and deISGylating enzyme, which antagonizes the innate immune response. SARS-CoV PL<sup>PRO</sup> is a member of the peptidase clan CA (family C16), with a classic catalytic triad in its active site composed of Cys112-His273-Asp287 (Báez-Santos, St. John, & Mesecar, 2015). The 3CL<sup>PRO</sup> generates various essential proteins for viral replication after cleavage of the polyprotein at 11 sites. This protease performs a crucial role in viral replication and is located at the 3'-end, differently encoding genes of structural/supplemental protein (Anand, Ziebuhr, Wadhwani, Mesters, & Hilgenfeld, 2003; Kumar, Tan, Wang, Lin, & Liang, 2016; Needle, Lountos, & Waugh, 2015; Qamar, Alqahtani, Alamri, & Chen, 2020). Among the glycoside flavonoids with 3CL<sup>PRO</sup> inhibition activity, Chen et al. (2006) described, by molecular docking experiments and enzymatic inhibitions assays, the potential of quercetin-3- $\beta$ -galactose (**37**), with IC<sub>50</sub> of 42.79  $\pm$  4.97  $\mu$ M, in a competitive mode. The same study investigated the binding interaction mode between the compound and the virus protease. Eight quercetin-3-O- $\beta$ -galactose derivatives were synthesized and after testing the inhibitory potentials, it was observed that the removal of hydroxyl groups (compounds **38–42**) decreases the activity. Acetylated glycosylic unity (compound **38**) is also unfavorable for activity and the addition of rhamnoside unity on the C-7 position of quercetin (compound **42**) did not affect the functionality against SARS-CoV. Changing the galactose to fucose (**39**), arabinose (**40**) or glucose (**41**) had no evident effect on inhibitor potency. All IC<sub>50</sub> values are represented in Table 1 (Chen et al., 2006).

**TABLE 1** Inhibitory activities of flavonoids **37**, **39–41** against SARS-CoV 3CL<sup>PRO</sup>

Flavonoid	Activity
Quercetin-3-O- $\beta$ -galactoside ( <b>37</b> )	SARS-CoV 3CL <sup>PRO</sup> Inhibitor IC <sub>50</sub> = 42.8 $\mu$ M
Quercetin-3-O- $\beta$ -fucoside ( <b>39</b> )	SARS-CoV 3CL <sup>PRO</sup> Inhibitor IC <sub>50</sub> = 24.1 $\mu$ M
Quercetin-3-O- $\beta$ -arabinoside ( <b>40</b> )	SARS-CoV 3CL <sup>PRO</sup> Protease inhibitor IC <sub>50</sub> = 31.6 $\mu$ M
Quercetin-3-O- $\beta$ -glucoside ( <b>41</b> )	SARS-CoV 3CL <sup>PRO</sup> Protease inhibitor IC <sub>50</sub> = 48.8 $\mu$ M

Puerarin (**43**), isolated from *Pichia pastoris*, showed low inhibitor activity against 3CL<sup>pro</sup>, with an IC<sub>50</sub> value of 381 μM. Compared with non-glycosylated derivative (daidzein - **19**), the study suggests that the presence or absence of a sugar moiety at ring A does not affect the activity (Nguyen et al., 2012). Glycoside flavonoids rhoifolin (**44**) and pectolinarin (**45**) were subjected to a molecular docking study and evaluated by Jo, Kim, Shin, and Kim (2020) against 3CL<sup>pro</sup>. The series of tested compounds showed high inhibitory values with IC<sub>50</sub> of 27.45 and 37.78 μM, respectively. These compounds have an α-L-rhamnopyranosyl β-D-glucopyranoside and L-rhamnopyranosyl β-D-glucopyranoside moieties. In addition, these sugar groups attached to position C-7 of the chromen-4-one occupy the S1 and S2 sites and S2 and S30 sites, unlike the two flavonols described above. The higher affinity of rhoifolin (**44**) may be due to orchestrated binding through S1, S2, and S3' sites (Jo et al., 2020). Studies carried out with roots of *Isatisidis indigotica*, allowed the identification of several compounds, including the flavanone hesperetin (**46**) and isoflavone daidzein (**19**), exhibiting IC<sub>50</sub> values against SARS-CoV 3CL<sup>pro</sup>, through cell-free cleavage assay, of 60 and 105 μM, respectively (Lin et al., 2005). Fractionation of extract from leaves of *Torreya nucifera* afforded four flavonoids: amentoflavone (**47**), bilobetin (**48**), ginkgetin (**49**), and sciadopityscin (**50**), which demonstrated 3CL<sup>pro</sup> inhibitory activity. The IC<sub>50</sub> values are 8.3, 72.3, 32.0, and 38.4 μM, respectively, and amentoflavone (**47**) is the most active (8.3 μM) (Ryu et al., 2010).

Nine alkylated chalcones (**51–59**) isolated from *Angelika keiskei* displayed in vitro activities against SARS-CoV proteases, including PL<sup>pro</sup>. 4-Hydroxyderricin (**51**), xanthoangelol (**52**), xanthoangelol F (**53**), xanthoangelol D (**54**), xanthoangelol E (**55**), xanthoangelol B (**56**), xanthoangelol G (**57**), and xanthokeistal A (**58**) showed IC<sub>50</sub> values of 26.0, 11.7, 5.6, 19.3, 1.2, 11.7, 46.4, and 21.1 μM against PL<sup>pro</sup>, respectively, with xanthoangelol E being the most active. An in silico molecular docking study was performed for compound **55**, showing that the hydroperoxyl group forms three hydrogen bonds at different binding sites. In this same study, isobavachalcone (**59**) displayed an IC<sub>50</sub> value of 13.0 μM against SARS-CoV PL<sup>pro</sup>. The inhibition mechanisms of flavonoids **52–59** were determined by the effect of the substances on the kinetics of substrate proteolysis and were determined to be non-competitive. Compound **59** was established as a mixed inhibition type (Park et al., 2016). As observed by the authors, the isoprene unit's length was not relevant for the observed activity. All activities are summarized in Table 2.

Molecular docking studies developed by Jo et al. (2019) suggested that herbacetin (**60**) occupies the S1 and S2 sites of MERS-CoV 3CL<sup>pro</sup>, and the hydroxyl group at C-7 position is essential for S1 binding site. Helichrysetin (**61**) exhibits relevant inhibitory activity and the authors suggest that the presence of a hydroxyl group at C-4 position is suitable for binding to MERS-CoV 3CL<sup>pro</sup> (Jo et al., 2019).

Fractionation of the bioactive extract from *Broussonetia papyfera* led to the isolation of flavonoids **62–71** (Table 3). When tested in vitro against SARS-CoV PL<sup>pro</sup>, brousochalcone B (**62**), brousochalcone A (**63**), 4-hydroxyisolonchocarpin (**64**), papyriflavonol A (**65**), 3'-(3-methylbut-2-enyl)-3',4',7-trihydroxyflavane (**66**), kazinol A (**67**), kazinol B (**68**), brousoflavan A (**69**), kazinol F (**70**), and kazinol

**TABLE 2** Inhibitory activities of flavonoids **51–59** against SARS-CoV 3CL<sup>pro</sup> and PL<sup>pro</sup>

Flavonoid	Activity
4-Hydroxyderricin ( <b>51</b> )	SARS-CoV Inhibitor IC <sub>50</sub> = 81.4 μM (3CL <sup>pro</sup> cell-free) IC <sub>50</sub> = 50.8 μM (3CL <sup>pro</sup> cell-based) IC <sub>50</sub> = 26.0 μM (PL <sup>pro</sup> )
Xanthoangelol ( <b>52</b> )	SARS-CoV Protease inhibitor IC <sub>50</sub> = 38.4 μM (3CL <sup>pro</sup> cell-free) IC <sub>50</sub> = 5.8 μM (3CL <sup>pro</sup> cell-based) IC <sub>50</sub> = 11.7 μM (PL <sup>pro</sup> )
Xanthoangelol F ( <b>53</b> )	SARS-CoV Protease inhibitor IC <sub>50</sub> = 34.1 μM (3CL <sup>pro</sup> cell-free) IC <sub>50</sub> = 32.6 μM (3CL <sup>pro</sup> cell-based) IC <sub>50</sub> = 5.6 μM (PL <sup>pro</sup> )
Xanthoangelol D ( <b>54</b> )	SARS-CoV Protease inhibitor IC <sub>50</sub> = 26.6 μM (3CL <sup>pro</sup> cell-free) IC <sub>50</sub> = 9.3 μM (3CL <sup>pro</sup> cell-based) IC <sub>50</sub> = 19.3 μM (PL <sup>pro</sup> )
Xanthoangelol E ( <b>55</b> )	SARS-CoV Protease inhibitor IC <sub>50</sub> = 11.4 μM (3CL <sup>pro</sup> cell-free) IC <sub>50</sub> = 7.1 μM (3CL <sup>pro</sup> cell-based) IC <sub>50</sub> = 1.2 μM (PL <sup>pro</sup> )
Xanthoangelol B ( <b>56</b> )	SARS-CoV Protease inhibitor IC <sub>50</sub> = 22.2 μM (3CL <sup>pro</sup> cell-free) IC <sub>50</sub> = 8.6 μM (3CL <sup>pro</sup> cell-based) IC <sub>50</sub> = 11.7 μM (PL <sup>pro</sup> )
Xanthoangelol G ( <b>57</b> )	SARS-CoV Protease inhibitor IC <sub>50</sub> = 129.8 μM (3CL <sup>pro</sup> cell-free) IC <sub>50</sub> = NT (3CL <sup>pro</sup> cell-based) IC <sub>50</sub> = 46.4 μM (PL <sup>pro</sup> )
Xanthokeistal A ( <b>58</b> )	SARS-CoV Protease inhibitor IC <sub>50</sub> = 44.1 μM (3CL <sup>pro</sup> cell-free) IC <sub>50</sub> = 9.8 μM (3CL <sup>pro</sup> cell-based) IC <sub>50</sub> = 21.1 μM (PL <sup>pro</sup> )
Isobavachalcone ( <b>59</b> )	SARS-CoV Protease inhibitor IC <sub>50</sub> = 39.4 μM (3CL <sup>pro</sup> cell-free) IC <sub>50</sub> = 11.9 μM (3CL <sup>pro</sup> cell-based) IC <sub>50</sub> = 13.0 μM (PL <sup>pro</sup> ); IC <sub>50</sub> = 7.3 μM (PL <sup>pro</sup> )

J (**71**) displayed moderate activities, with IC<sub>50</sub> values of 11.6, 9.2, 35.4, 3.7, 35.8, 66.2, 31.4, 20.4, 27.8 and 15.2 μM, respectively. The prenylated flavonol derivative **65** showed the highest activity. It was more potent against the catalytic activity of SARS-CoV PL<sup>pro</sup> than flavone derivatives such as kaempferol (IC<sub>50</sub> = 16.3 μM), quercetin (IC<sub>50</sub> = 8.6 μM), and quercetin-O-β-galactose (IC<sub>50</sub> = 51.9 μM), probably due to strong hydrophobic interactions with the enzyme. Kinetic studies determined all compounds as non-competitive inhibitor types.

**TABLE 3** Inhibitory activities of flavonoids **62–71** against SARS-CoV and MERS-CoV proteases

Flavonoid	Activity
Brousochalcone B (62)	SARS-CoV Protease inhibitor IC <sub>50</sub> = 57.8 μM (3CL <sup>pro</sup> <sub>cell-free</sub> ) IC <sub>50</sub> = 11.6 μM (PL <sup>pro</sup> ) MERS-CoV Protease inhibitor IC <sub>50</sub> = 27.9 μM (3CL <sup>pro</sup> ) IC <sub>50</sub> = 112.9 μM (PL <sup>pro</sup> )
Brousochalcone A (63)	SARS-CoV Protease inhibitor IC <sub>50</sub> = 88.1 μM (3CL <sup>pro</sup> ) IC <sub>50</sub> = 9.2 μM (PL <sup>pro</sup> ) MERS-CoV Protease inhibitor IC <sub>50</sub> = 36.2 μM (3CL <sup>pro</sup> ) IC <sub>50</sub> = 42.1 μM (PL <sup>pro</sup> )
4-Hydroxyisolonchocarpin (64)	SARS-CoV Protease inhibitor IC <sub>50</sub> = 202.7 μM (3CL <sup>pro</sup> ) IC <sub>50</sub> = 35.4 μM (PL <sup>pro</sup> ) MERS-CoV Protease inhibitor IC <sub>50</sub> = 193.7 μM (3CL <sup>pro</sup> ) IC <sub>50</sub> = 171.6 μM (PL <sup>pro</sup> )
Papyriflavonol A (65)	SARS-CoV Protease inhibitor IC <sub>50</sub> = 103.6 μM (3CL <sup>pro</sup> ) IC <sub>50</sub> = 3.7 μM (PL <sup>pro</sup> ) MERS-CoV Protease inhibitor IC <sub>50</sub> = 64.5 μM (3CL <sup>pro</sup> ) IC <sub>50</sub> = 112.5 μM (PL <sup>pro</sup> )
3'-(3-methylbut-2-enyl)-3',4',7-trihydroxyflavane (66)	SARS-CoV Protease inhibitor IC <sub>50</sub> = 30.2 μM (3CL <sup>pro</sup> ) IC <sub>50</sub> = 35.8 μM (PL <sup>pro</sup> ) MERS-CoV Protease inhibitor IC <sub>50</sub> = 34.7 μM (3CL <sup>pro</sup> ) IC <sub>50</sub> = 48.8 μM (PL <sup>pro</sup> )
Kazinol A (67)	SARS-CoV Protease inhibitor IC <sub>50</sub> = 84.8 μM (3CL <sup>pro</sup> ) IC <sub>50</sub> = 66.2 μM (PL <sup>pro</sup> ) MERS-CoV Protease inhibitor NA (3CL <sup>pro</sup> ) IC <sub>50</sub> = 13.0 μM (PL <sup>pro</sup> )
Kazinol B (68)	SARS-CoV Protease inhibitor IC <sub>50</sub> = 233.3 μM (3CL <sup>pro</sup> ) IC <sub>50</sub> = 31.4 μM (PL <sup>pro</sup> ) MERS-CoV Protease inhibitor NA (3CL <sup>pro</sup> ) IC <sub>50</sub> = 88.5 μM (PL <sup>pro</sup> )

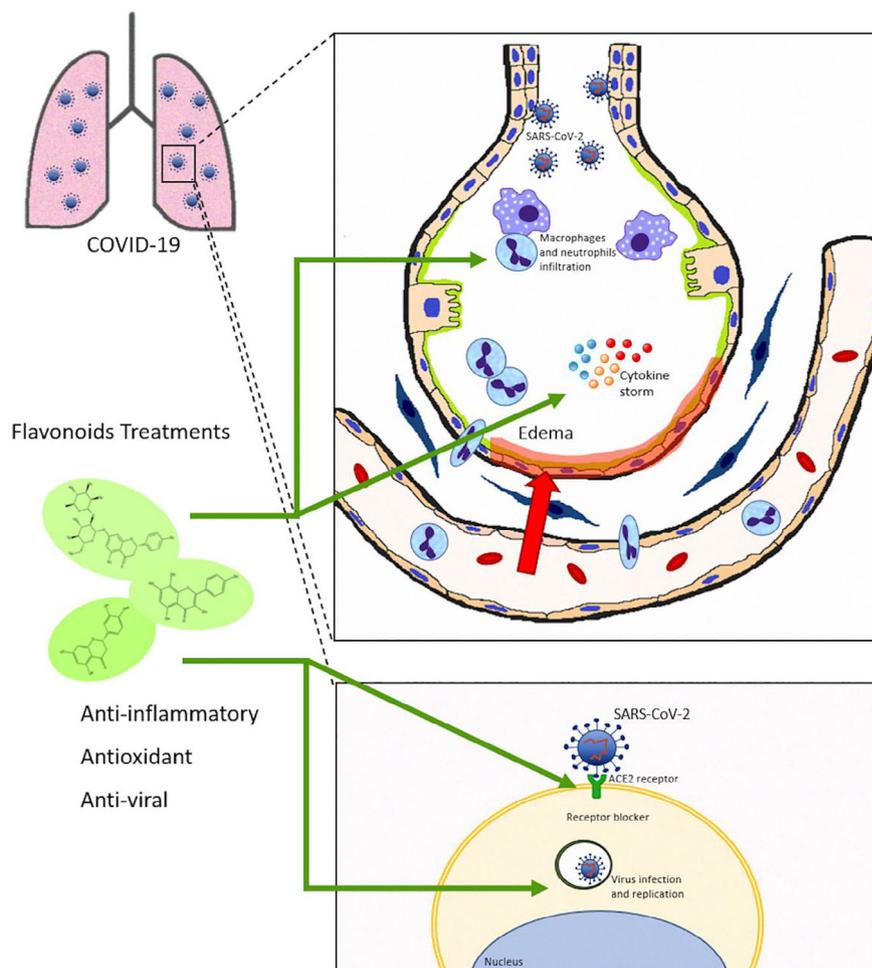
**TABLE 3** (Continued)

Flavonoid	Activity
Brousoflavan A (69)	SARS-CoV Protease inhibitor IC <sub>50</sub> = 92.4 μM (3CL <sup>pro</sup> ) IC <sub>50</sub> = 30.4 μM (PL <sup>pro</sup> ) MERS-CoV Protease inhibitor IC <sub>50</sub> = 125.7 μM (3CL <sup>pro</sup> ) IC <sub>50</sub> = 49.1 μM (PL <sup>pro</sup> )
Kazinol F (70)	SARS-CoV Protease inhibitor IC <sub>50</sub> = 43.3 μM (3CL <sup>pro</sup> ) IC <sub>50</sub> = 27.8 μM (PL <sup>pro</sup> ) MERS-CoV Protease inhibitor IC <sub>50</sub> = 135.0 μM (3CL <sup>pro</sup> ) IC <sub>50</sub> = 39.5 μM (PL <sup>pro</sup> )
Kazinol J (71)	SARS-CoV Protease inhibitor IC <sub>50</sub> = 64.2 μM (3CL <sup>pro</sup> ) IC <sub>50</sub> = 15.2 μM (PL <sup>pro</sup> ) MERS-CoV Protease inhibitor IC <sub>50</sub> = 109.2 μM (3CL <sup>pro</sup> ) IC <sub>50</sub> = 55.0 μM (PL <sup>pro</sup> )

When tested for activity against MERS-CoV PL<sup>pro</sup>, none showed high potential, with IC<sub>50</sub> values between 39.5 and 171.6 μM (Park et al., 2017).

Fractionation of bioactive extract from *Paulownia tomentosa* fruits led to the isolation of flavonoids **72–83**. Evaluated against SARS-CoV PL<sup>pro</sup>, all compounds showed inhibitory activity. Tomentin A (**72**), tomentin B (**73**), tomentin C (**74**), tomentin D (**75**), tomentin E (**76**), 3'-O-methyl-diapicol (**77**), 4'-O-methoxydiapicol (**78**), 3'-O-methyl-diapicolone (**79**), 4'-O-methyl-diapicolone (**80**), mimulone (**81**), diapicolone (**82**), and 6-geranyl-4',5,7-trihydroxy-3',5'-dimethoxyflavanone (**83**) displayed IC<sub>50</sub> values of 6.2, 6.1, 11.6, 12.5, 5.0, 9.5, 9.2, 13.2, 12.7, 14.4, 10.4, and 13.9 μM, respectively. Compounds **72–76**, bearing unusual 3,4-dihydro-2H-pyran structures, were more effective in inhibiting the enzyme than the cyclization precursors (Cho et al., 2013). This series of compounds allowed the authors to infer that a 3,4-dihydro-2H-pyran moiety is more effective at inhibiting 3CL<sup>pro</sup> expression than the open ring precursors. The extract from *Psoralea corylifolia* seeds was subjected to fractionation to afford six related flavonoids (**59** and **84–88**). These compounds were then evaluated for potential SARS-CoV PL<sup>pro</sup> inhibition in vitro. Bavachinin (**84**), neobavaisoflavone (**85**), 4'-O-methylbavachalcone (**86**), and corylinin (**87**) showed moderate IC<sub>50</sub> values of 38.4, 18.3, 10.1, and 32.3 μM, respectively, while isobavachalcone (**59**) and psoralidin (**88**) were the most active compounds, with IC<sub>50</sub> values of 7.3 and 4.2 μM, respectively. These results suggest that *P. corylifolia* can be considered a source of potent PL<sup>pro</sup> inhibitors, and the strongest ones were isobavachalcone and psoralidin. Enzyme kinetic assay determined that all compounds possess a mixed inhibition

**FIGURE 3** Possible effects of flavonoids on COVID-19-induced acute lung injury: COVID-19 affects several organs, especially the pulmonary system. Severe COVID-19 is characterized by a cytokine storm and acute lung inflammation that can progress to acute lung injury and systemic inflammation. Acute lung injury is well characterized by endothelium and/or epithelial injury, macrophage activation, neutrophil recruitment, and oxidative stress as well as high cytokine release. The binding of SARS-CoV-2 to ACE2 in epithelial cells induces infection and virus replication. The flavonoid has well-described antiinflammatory, antioxidant, and antiviral effects. The evidence reviewed in the literature shows that flavonoid could be a potential therapeutic target for COVID-19, since it inhibits the cytokine storm and lung inflammation. In addition, evidence suggests that it can block the entry and replication of the virus, and should be further explored



mode (Kim et al., 2014). Nguyen et al. (2012) compared the activity of ampelopsin (**89**), epigallocatechin gallate (**90**), epigallocatechin (**91**), and gallic acid (**92**), from *Pichia pastoris* (Nguyen et al., 2012). The results suggested that compounds **90** and **92** possess stronger 3CL<sup>pro</sup> inhibitory activity than **89** and **91**, with IC<sub>50</sub> values of 73 and 47  $\mu$ M for **90** and **92**, respectively, and 364  $\mu$ M for **89**. Only an inhibitory percentage of 5.4% at 200  $\mu$ M was observed for **91**.

Using molecular docking assays, theaflavin (**93**) can bind in catalytic pockets of RNA-dependent RNA-polymerase (RdRp) of MERS-CoV, SARS-CoV, and SARS-CoV-2 (Lung et al., 2020). In this way, this compound could be considered a lead compound for inhibitors targeting CoVs RdRp (Lung et al., 2020). A study demonstrated that 3-theaflavin-3-gallate (**94**) and theaflavin-3,3'-digallate (**95**), both present in black tea, were effective against SARS-CoV 3CL<sup>pro</sup>, with IC<sub>50</sub> values of 7.0 and 9.5  $\mu$ M. This suggests that black tea could prevent or alleviate coronavirus infection (Chen et al., 2005). Studies carried out by Zhuang et al. (2009) with extracts from *Cinnamomi cortex* describe inhibition in wild-type SARS-CoV (Zhuang et al., 2009). It was possible to isolate from this extract procyanidin A2 (**96**), procyanidin B2 (**97**), and dimer cinnamtannin B1 (**98**), showing overall moderate inhibitory effects with IC<sub>50</sub> values of 120.7, 161.1, and 32.9  $\mu$ M, respectively (Zhuang et al., 2009).

SARS-CoV N protein envelopes the genomic RNA, and as such, has a crucial role in the virus particle assembly. It may cause apoptosis of the host cells, upregulate the proinflammatory cytokine production and block innate immune responses. In addition, it has a significant role in replication for this virus and is considered a central target for anti-SARS drugs. An inhibitor screening of this protein was performed on a biochip platform, with high sensitivity and rapid response. In this work, (–)-gallic acid gallate (**92**) and (–)-catechin gallate (**99**) showed high activity. Both compounds, at 0.005  $\mu$ g/mL, diminished the binding affinity in a concentration-dependent manner. More than 40% inhibition was displayed at a concentration of 0.05  $\mu$ g/mL on the biochip platform for **92** and **99**. Other flavonoids including kaempferol (**100**) and quercetin (**15**), showed no inhibitory activity at the tested concentrations (Roh, 2012).

The flavonoid juglanin (**101**) was shown to inhibit SARS-CoV 3-a-mediated current, with an IC<sub>50</sub> value of 2.5  $\mu$ M. The activity of this cation-selective channel can be expressed in the infected cells and virus release (Schwarz et al., 2014).

In summary, flavonoids' favorable effects are related to the antiinflammatory, antioxidant, immunomodulatory, and anti-viral effects, suggesting that flavonoids can be a promising treatment strategy for conventional drugs against COVID-19.

## 4 | DISCUSSION AND CONCLUSIONS

A range of studies is, globally, currently trying to find an efficient treatment and/or a vaccine to treat or prevent COVID-19, a pandemic that has so far caused hundreds of thousands of deaths and has crippled the global economy. In the present review, we reported the biological effects of several flavonoids inhibiting some coronavirus proteins or counteracting lung inflammation and cytokine storm, which is a critical consequence of SARS-CoV-2. These polyphenolic compounds, isolated from different plants, have been used to treat numerous viral diseases successfully and can be used, associated with other pharmacological treatments, in the treatment of COVID-19 as well. Both flavonoids and other compounds derived from plants can also modulate the immune system to improve the organism defense, modulating macrophage profile and natural killer cells, and increasing antiinflammatory mechanisms (Tutunchi et al., 2020).

Based on the different structures of flavonoids **1–101**, some structure–activity relationships (SAR) could be established. Initially, it was observed that glycosylated derivatives exhibited improved biological effects than their aglycone derivatives, which could be explained, at least in part, by the possibility of formation of different hydrogen bonds between the flavonoid and catalytic site of other enzymes (Ryu et al., 2010). Considering the structure of flavonoid moiety, the more active derivatives were flavonols, suggesting that an  $\alpha,\beta$ -unsaturated system (double bond at C-2/C-3 and carbonyl group at C-3) is associated to the presence of an oxygen atom at C-3, plays an important role in the activity. Furthermore, it was observed that the presence of a catechol unity in the ring B (positions C-3' and C-4') of different flavonoids is associated with higher potential in relation to related derivatives displaying no substituents at ring B or those presenting only one hydroxyl or methoxyl group at C-4' position. Considering the effects of compounds **47–50** and the pronounced activity of flavonoid **47**, it is possible to suggest that free hydroxyl groups are crucial since derivatives **48–50**, which exhibited methoxyl groups, displayed reduced activity. As reported in the literature (Ryu et al., 2010), the catechol unity is related to the interactions of bioactive compounds and catalytic site by hydrogen bond formation of different enzymes SARS-CoV or MERS-CoV protease inhibitors, associated with coronavirus replication. Considering bioflavonoids **47–50**, interesting structural-activity relationships could be established, especially the methylation of hydroxyl groups at C-7' and C-4', which cause a reduction in the inhibitory activity. However, methoxyl at C-7 increases the potency, suggesting that methoxyl groups' position in the structures of these related bioflavonoids is associated with their inhibitory potential of SARS-CoV 3CL<sup>PRO</sup> (Russo et al., 2020; Ryu et al., 2010). Considering chalcone derivatives **51–64**, the biological effect (SARS-CoV protease inhibitor) seems to be associated with the presence of prenyl unities at different position of C<sub>6</sub>C<sub>3</sub>C<sub>6</sub> moiety – this initial analysis also suggested that the presence of hydroxyl group at C-4' is important to the activity – in addition, it is essential to mention that the acyclic prenyl unity at C-3 seen to be crucial to activity of related compounds since compound **64**, a chromene, exhibited reduced potential. A similar profile was observed to prenylated flavanes **66–69**

since the effect of compounds, which showed an acyclic unity (**66** and **67**) were able to inhibit SAR-CoV and MERS-CoV more efficiently in comparison to chromene derivatives **68** and **69**. In addition, considering the structures of biflavones **47–50**, biflavonols **93–98**, and their inhibitory effects of SARS-CoV 3CL<sup>PRO</sup> enzymes, it was observed a positive influence of dimerization (Islam et al., 2020; Ryu et al., 2010).

Studies using molecular docking showed that rutin, which was approved by NMPA (National Medical Products Administration), exhibited the best effect in the binding affinity to inhibit SARS-CoV-2 compared to other compounds (Xu et al., 2020). Some authors have also shown that certain flavonoids can interact with the receptor binding of the SARS-CoV-2 using *in silico* analysis (Istifli et al., 2020). In this computational study, the group of flavonoids anthocyanidins, isoflavones, and flavanones showed improved interaction with the target proteins, in special (–)-epicatechin gallate. Basu et al. (2020) also showed that the structure of ACE2 and spike protein fragment becomes unstable in the presence of hesperidin, suggesting that this compound can have effects on the virus entry. Besides, the effects evaluated by *in silico* studies showing possible effects of flavonoids in the ACE2 and Spike interaction, we have to consider that flavonoids have an antiinflammatory effect well known, avoiding or reducing lung inflammation and the cytokine storm induced by SARS-CoV-2, as shown in Figure 3. In this regard, our group and others showed that flavonoids can inhibit NF- $\kappa$ B and MAP kinase pathways, and cellular signaling involved in ALI. Moreover, flavonoids can reduce cytokine release in the lung and the neutrophils and macrophage recruitment and activation, respectively, which could be interesting for inhibiting cytokine storm and acute inflammation. We have previously shown that sakuranetin inhibits several features of ALI induced by LPS in mice, improving respiratory function and reducing the weight loss induced by systemic infection (Bittencourt-Mernak et al., 2017). Although COVID-19-induced ALI has a different mechanism from LPS-induced ALI, the cytokine storm and lung injury have similar features.

Therefore, this review emphasized flavonoids' ability to inhibit several features of COVID-19, which may help researchers working on COVID-19 drug discovery, an urgent need under the continuing spread of COVID-19. Of course, *in vitro* testing of the drug candidates is necessary - however, this review may prove valuable for exploring and developing novel natural anti-COVID-19 therapeutic agents in the future, which can be associated with other drugs or not. However, further research and more detailed pharmacological investigations *in vivo*, including PK/PD studies, must be performed to develop new drugs to treat coronavirus diseases, such as COVID-19.

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### CONFLICT OF INTEREST

The authors have no conflicts of interest to declare related to the data shown on this publication.

## DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study since it is a review paper

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